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CHAPTER 1

General introduction and outline thesis
INTRODUCTION

Heart failure (HF) remains one of the major public health problems in developed countries. In United States, nearly 6 million patients have HF symptoms and 500,000 new patients are diagnosed yearly.\(^1\) Recently, important advances in HF therapy, such as cardiac resynchronization therapy (CRT), have improved the outcome of these patients.\(^2\) However, the prognosis remains poor with a 5-year mortality of 42.3% after hospitalization for HF.\(^1\)

Selection of HF patients who are candidates for device therapies (such as CRT) is crucial to optimize the therapy results while minimizing the risk of potential complications (including lack of response to the device therapy). Advanced imaging techniques have helped to better understand the pathologic substrate of heart failure patients and have provided novel insight into the determinants of response to therapy.

The study of cardiac mechanics and in particular, left ventricular (LV) strain and twist are important aspects of cardiac mechanics.\(^3,4\) LV strain refers to the deformation of the LV, which occurs in the longitudinal, circumferential and radial directions. Furthermore, the spiral architecture of LV myofibers lead to a characteristic motion of rotation of the LV apex and base in opposite directions, counterclockwise and clockwise as viewed from the LV apex, respectively. The opposite rotation of LV apex and base leads to a LV systolic wringing motion during systole referred to as twist or torsion. In particular, LV twist is the net difference at isochronal time points between apex and base in the rotation angle along LV longitudinal axis, whereas LV torsion is LV twist indexed to the distance between LV apex and LV base.\(^5\) This characteristic motion of the LV contributes significantly to LV systolic and diastolic function. In the last decade, assessment of myocardial strain and twist has emerged as novel LV functional parameters for risk stratification of patients with structural heart disease.

Nowadays, echocardiography and magnetic resonance imaging allow the study of LV mechanics. However, echocardiography remains as the imaging technique of first choice due to its wide availability and less time-consuming analysis compared with magnetic resonance imaging. Two-dimensional (2D) speckle tracking, tissue Doppler imaging and, less frequently, calibrated integrated backscatter imaging, are the echocardiographic techniques to assess several aspects of LV mechanics. From 2D speckle tracking echocardiography, the assessment of active myocardial deformation in multiple directions (radial, circumferential and longitudinal) and LV twist can be obtained. From tissue Doppler imaging, velocities and indirect information on deformation may be derived. Integrated backscatter, finally, through the analysis of assessment of myocardial ultrasound reflectivity, may quantify the percentage of myocardial fibrosis.
2D speckle tracking echocardiography

Based on 2D gray scale echocardiographic images, the myocardium exhibit natural acoustic markers or speckles that can be tracked frame-to-frame using speckle tracking software. Speckles are randomly distributed within the myocardium and the specific distribution of the speckles provides a distinguished pattern to each myocardial region, such as a fingerprint. The movement of the speckles along the cardiac cycle is tracked frame-to-frame independently from the ultrasound beam insonation angle permitting the evaluation of myocardial contraction/relaxation along the circumferential, longitudinal and radial direction. The LV contraction in these 3 directions leads to rotation movement of the left ventricle. The speckle tracking software calculates LV rotation from the apical and basal short-axis images as the average angular displacement of the 6 standard segments referring to the ventricular centroid, frame by frame. Counterclockwise rotation is marked as positive value and clockwise rotation as negative value when viewed from the LV apex. LV twist is defined as the net difference (in degrees) of apical and basal rotation at isochronal time points.

Figure 1. Examples of left ventricular (LV) twist in normal control (panel A) and in heart failure patient (panel B). In both panels, the upper parts represent apical and basal rotations and the lower parts represent LV twist calculation after exporting the data to a spreadsheet program (Excel 2003; Microsoft Corporation, Redmond, Washington). AVC: aortic valve closure. AVO: aortic valve opening.
Tissue Doppler imaging

Tissue Doppler imaging (TDI) permits the assessment of low velocities of the myocardium along the cardiac cycle. TDI can be applied with pulsed-wave Doppler or with color-coded TDI. While pulsed-wave TDI permits assessment of one myocardial region on-line, color-coded TDI permits assessment of several regions simultaneously off-line. In contrast to 2D speckle tracking echocardiography, the measurement of myocardial velocities with TDI is insonation angle dependent and therefore, the analysis is frequently limited to the basal and midventricular regions. From spatial derivation of myocardial velocities, regional strain rate can be obtained and from further temporal integration of strain rate, myocardial strain can be obtained.

The assessment of myocardial velocities and the time elapsed between electrical and mechanical (velocities) phenomena provide an estimate of the electromechanical delay within the myocardium. It has been hypothesized that the time delay between the P-wave on the surface ECG and the A’ wave on TDI (total atrial conduction time) may reflect the amount of myocardial fibrosis. Total atrial conduction time may be estimated with color-coded tissue Doppler images by first placing the sample size on the LA lateral wall just above the mitral annulus; next the PA-TDI duration was measured.
size on the LA lateral wall just above the mitral annulus. Next, the time-interval from the onset of the P-wave on lead II of the electrocardiogram (on echocardiographic images) to the peak of $A'_{LATERAL}$ wave (PA-TDI duration) is measured and an estima-
tion of atrial conduction time is obtained. In HF patients, this TA-TDI duration has been associated with increased risk of atrial fibrillation at follow-up.

**Integrated backscatter**

Calibrated integrated backscatter (IB) is a parameter based on gray-scale 2D images which evaluates myocardial ultrasound reflectivity. In the heart, the pericardium is the anatomic structure with the highest content of fibrosis and with the highest ultrasound reflectivity; whereas blood pool has the lowest ultrasound reflectivity since no fibrous tissue exists. The myocardium shows an intermediate ultrasound reflectivity and this reflectivity may increase together with the amount of fibrosis. Gray-scale 2D images may be obtained at parasternal long-axis view, with frame rates between 80 and 120 frames/s. A fixed region of interest is then positioned in the mid-myocardium of the antero-septal and posterior walls of the LV and a fixed region of interest is positioned in the pericardium. A measure of myocardial ultrasound reflectivity or tissue density is obtained with calibrated IB by subtracting pericardial IB intensity from myocardial IB intensity of the LV antero-septal and LV posterior walls.

**Objectives and Outline of the Thesis**

The objectives of this thesis were to investigate the role of LV mechanics in the assessment of HF patients who are candidates to CRT and to evaluate the prognostic value of parameters derived from the several imaging techniques to assess LV mechanics.

In **Part I**, the study of cardiac mechanics is applied to HF patients in order to: 1. distinguish LV mechanics between the different aetiologies of HF (Chapter 3); 2. to investigate the beneficial effects of CRT on long-term outcome of HF patients (Chapters 4-6); 3. how to optimize the response to CRT (Chapter 7).

Finally, **Part II** provides an overview of the several parameters, clinical and echocardiographic, that influence the outcome of HF patients. Specifically, Chapter 8 demonstrates that echocardiographic response to CRT is an independent predictor of long-term outcome over other well-established prognostic indices of HF. Chapter 9 focuses on the assessment of risk of ventricular tachyarrhythmias in HF patients based on LV cardiac mechanics. Chapter 10 shows that LV global longitudinal strain is strong prognostic determinant of patients with ischemic HF. Finally, Chapter 11 underscores the relevance of electromechanical delay within the atrial myocardium as a risk factor for atrial fibrillation in HF patients with an implantable cardioverter-defibrillator.
REFERENCES


